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Reorganization and Preservation of Motor Control of the Brain in Spinal Cord Injury: A Systematic Review

Kristen J. Kokotilo,^{1,2} Janice J. Eng,^{1–4} and Armin Curt^{1,4,5}

Abstract

Reorganization of brain function in people with CNS damage has been identified as one of the fundamental mechanisms involved in the recovery of sensorimotor function. Spinal cord injury (SCI) brain mapping studies during motor tasks aim for assessing the reorganization and preservation of brain networks involved in motor control. Revealing the activation of cortical and subcortical brain areas in people with SCI can indicate principal patterns of brain reorganization when the neurotrauma is distal to the brain. This review assessed brain activation after SCI in terms of intensity, volume, and somatotopic localization, as well as preservation of activation during attempted and/or imagined movements. Twenty-five studies meeting the inclusion criteria could be identified in Medline (1980 to January 2008). Relevant characteristics of studies (level of lesion, time after injury, motor task) and mapping techniques varied widely. Changes in brain activation were found in both cortical and subcortical areas of individuals with SCI. In addition, several studies described a shift in the region of brain activation. These patterns appeared to be dynamic and influenced by the level, completeness, and time after injury, as well as extent of clinical recovery. In addition, several aspects of reorganization of brain function following SCI resembled those reported in stroke. This review demonstrates that brain networks involved in different demands of motor control remain responsive even in chronic paralysis. These findings imply that therapeutic strategies aimed at restoring spinal cord function, even in people with chronic SCI, can build on preserved competent brain control.

Key words: motor; neuroimaging; plasticity; reorganization; SCI

Introduction

SPIINAL CORD INJURY (SCI) can be a devastating injury that partially or fully disconnects the spinal cord from the brain. In Canada, an estimated 900 people experience SCI each year (Canadian Paraplegic Association, 2008) and worldwide, the reported incidence of SCI lies between 10.4 and 83 per million inhabitants per year (Wyndaele and Wyndaele, 2006). Approximately 50% of patients are diagnosed with tetraplegia and experience paralysis of all four limbs, while the remaining are diagnosed with paraplegia affecting the lower limbs (Canadian Paraplegic Association, 2008). In addition to the lesion level, SCI is classified as complete or incomplete based on the amount of residual motor activity or sensation present below the spinal lesion (Maynard et al., 1997). The impairment of motor, sensory, and autonomic function in SCI can have a devastating effect on function (Yu, 1998). Tremendous efforts are undertaken to

identify the clinically most important mechanisms involved in recovery after SCI.

In brain injuries (e.g., cerebrovascular disease, traumatic brain injury), one mechanism that the central nervous system uses to compensate for its loss is by neural plasticity. For example, after cortical injury in monkeys the greater the injury to the primary motor cortex, the greater the reorganization of intact areas such as the premotor cortex (Frost et al., 2003). Similarly, reorganization occurs after SCI and numerous animal studies have demonstrated that cortical areas responsible for movement and sensation of intact body parts have a tendency to enlarge and invade areas responsible for a lost target after SCI (Raineteau and Schwab, 2001).

While studies in animals have provided invaluable insights into how the brain reorganizes after neurological injury, the recent advances of neuroimaging and brain mapping have enabled study of neural plasticity in the human brain. Over the years, a variety of non-invasive techniques have emerged,

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such as functional magnetic resonance imaging (fMRI), positron emission topography (PET), electroencephalography (EEG), transcranial magnetic stimulation (TMS), and magnetoencephalography (MEG), which permit insights into brain activation while movement is taking place. The literature has demonstrated that in human brain injury, such as stroke, reorganization occurs in both cortical and subcortical regions while performing movement (Teasell et al., 2005; Ward et al., 2003). Likewise, after SCI, neuroimaging studies have suggested that there is a pattern of reorganization of motor areas in the brain that occurs during movement (Turner et al., 2003). Unlike cortical injuries, the brain remains largely intact after SCI, providing a unique opportunity to use neuroimaging-mapping techniques to examine cortical reorganization in an intact brain after a distant CNS neurotrauma.

Recent neuroimaging-mapping studies have published patterns of brain reorganization that occur during movement after SCI. However, it is difficult to determine the effects of SCI on brain reorganization with individual studies because of varying protocols (e.g., different motor tasks, types of SCI, time of injury) and often varying and even conflicting results. Alternatively, reviewing all the relevant literature allows us to place a single study within the context of other findings to identify commonalities and conflicts in the literature. Thus, this review systematically analyzed published neuroimaging-mapping studies of brain activation after SCI to assess intensity, volume, and somatotopic localization, as well as preservation of brain activation during attempted and/or imagined movements.

Materials and Methods

The Medline database (1980–2008) was used to search the literature. The search was limited to journal articles written in English and containing human subjects. Abstracts, conference proceedings, and case studies were excluded. Searches were performed using combinations of the key words: SCI paired with fMRI, EEG, MEG, and PET. We omitted TMS studies from the search for a number of reasons. Our intent was to examine activation during voluntary control and a task that involved active or attempted movement was required. In addition, the majority of TMS studies in the literature were not focused on changes in sensorimotor networks of the brain, in contrast to the mapping studies included in this review. Most of the TMS studies examined the changes in thresholds and intensity within very select pathways (e.g., corticospinal tract) where the results are also dependent on spinal and peripheral neural pathways. Lastly, TMS studies focus on only very specific areas of the brain with little or no clear presentation of activation of secondary and subcortical motor areas.

Our inclusion criteria were as follows: (1) a population of people with SCI with the number of subjects greater than 2; (2) the use of neuroimaging-mapping techniques to assess brain activation in motor areas; and (3) the use of motor activation paradigms involving active (executed or attempted) or imagined or imaginary movements. A total of 471 papers were identified, of which 395 were not relevant (e.g., no subjects with SCI; animal studies). Seventy-six abstracts were reviewed in detail. Figure 1 depicts the sequence of the selection process used to identify a total of 24 articles describing brain plasticity following onset of SCI.

Results

Subject characteristics of reviewed studies

The number of individuals with SCI in each study ranged widely from 4 to 44; however the majority of studies (22/24) included 5 to 15 individuals with SCI. Age of subjects with SCI ranged from 17 to 67 and time since injury ranged from 0.25 months to 33 years post-injury. For those studies specifying gender of subjects, one third of studies used only males, while less than one half used a combination of males and females, with males comprising 70% of the subjects. Among studies, the level and extent of SCI lesions were also variable, with seven articles involving cervical lesions exclusively (Astolfi et al., 2007; Fallani et al., 2007; Jurkiewicz et al., 2007; Mattia et al., 2006; Mikulis et al., 2002; Shoham et al., 2001; Winchester et al., 2005); five articles involving lesions in the cervical to thoracic range (Cramer et al., 2005, 2007; Green et al., 1998, 1999; Turner et al., 2001); eight articles involving lesions in the thoracic to lumbar range (Alkadhi et al., 2005; Curt et al., 2002a; Halder et al., 2006; Hotz-Boendermaker et al., 2008; Lotze et al., 1999, 2006; Sabbah et al., 2002; Turner et al., 2003); three articles involving lesions in the cervical to lumbar range (Bruehlmeier et al., 1998; Curt et al., 2002b; Lacourse et al., 1999); and one article that did not specify lesion location (Castro et al., 2007). In terms of completeness of injury, five articles included complete injuries exclusively (Alkadhi et al., 2005; Castro et al., 2007; Cramer et al., 2005; Curt et al., 2002b; Turner et al., 2003); one article involved incomplete injuries exclusively (Winchester et al., 2005); 13 articles included both complete and incomplete injuries (Cramer et al., 2005, 2007; Green et al., 1998, 1999; Halder et al., 2006; Hotz-Boendermaker et al., 2008; Jurkiewicz et al., 2007; Lacourse et al., 1999; Lotze et al., 2006; Mattia et al., 2006; Mikulis et al., 2002; Sabbah et al., 2002; Turner et al., 2001); and four articles did not specify the completeness of injury (Astolfi et al., 2007; Bruehlmeier et al., 1998; Fallani et al., 2007; Shoham et al., 2001).

Imaging-mapping modalities utilized in reviewed studies

In the present review, a number of imaging modalities were used in the included articles, with the primary modality being fMRI (14 articles) (Alkadhi et al., 2005; Cramer et al., 2005, 2007; Curt et al., 2002a; Hotz-Boendermaker et al., 2008; Jurkiewicz et al., 2007; Lotze et al., 1999, 2006; Mikulis et al., 2002; Sabbah et al., 2002; Shoham et al., 2001; Turner et al., 2001, 2003; Winchester et al., 2005) and the others including EEG (eight articles) (Astolfi et al., 2007; Castro et al., 2007; Fallani et al., 2007; Green et al., 1998, 1999; Halder et al., 2006; Lacourse et al., 1999; Mattia et al., 2006) and PET (two articles) (Bruehlmeier et al., 1998; Curt et al., 2002b). The imaging and mapping modalities cited in the studies measure plasticity of the brain differently. In brief, fMRI and PET measure neural activation indirectly via change in cerebral blood flow or metabolic activity while EEG records electrical impulses from the brain through electrodes placed on the scalp.

Motor tasks utilized in reviewed studies

Although all studies were chosen to encompass use of motor activation paradigms, there was wide variation to the motor tasks utilized in the studies. In motor paradigms where

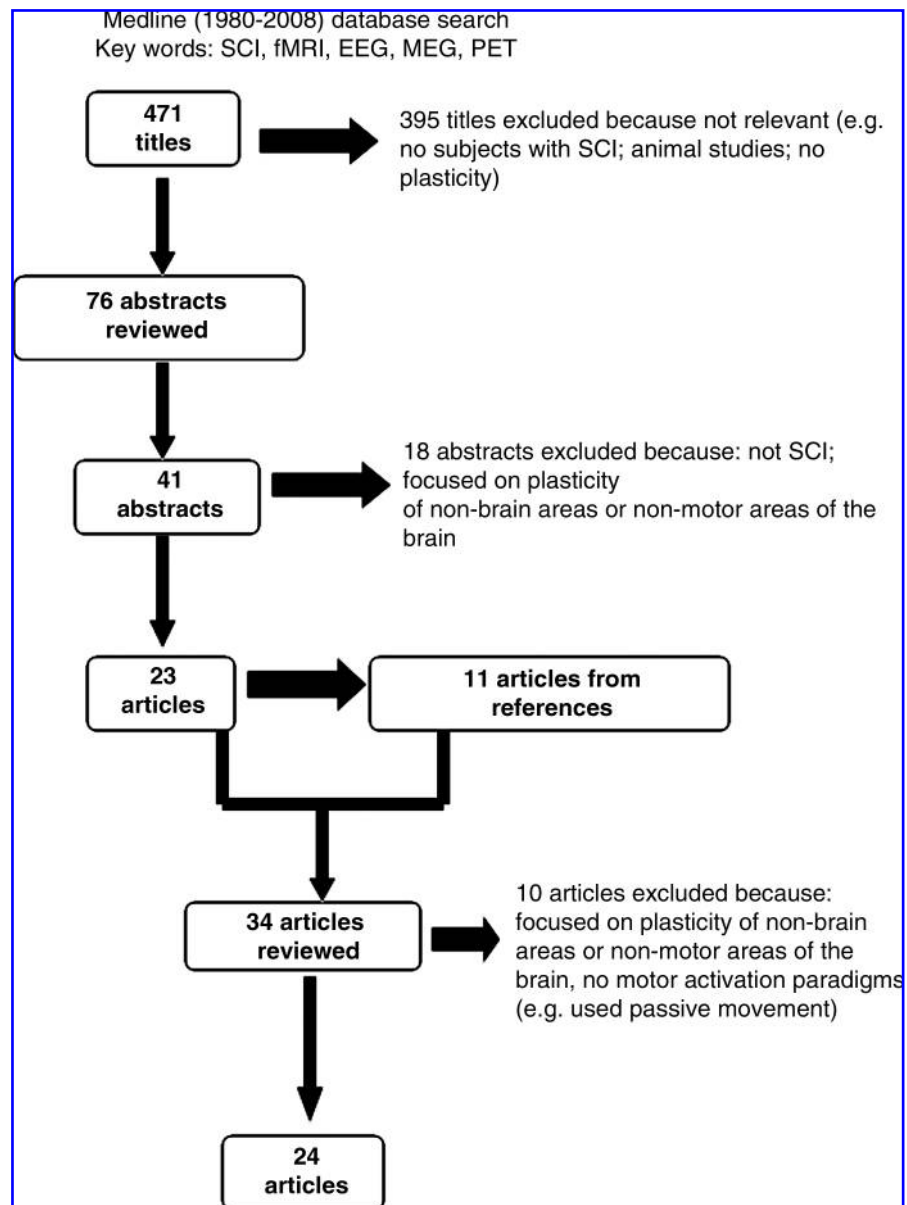


FIG. 1. Sequence of the selection process used to find articles describing brain plasticity following onset of SCI within inclusion criteria.

the individual attempted to move or execute movement, upper limb, lower limb, and facial tasks were included. Upper limb motor tasks included wrist or hand movement (Bruehlmeier et al., 1998; Curt et al., 2002a, 2002b; Jurkiewicz et al., 2007; Lacourse et al., 1999; Mikulis et al., 2002; Turner et al., 2003); finger movement (Curt et al., 2002a; Green et al., 1998, 1999; Lotze et al., 1999, 2006; Shoham et al., 2001); pinch grip (Lotze et al., 2006); and elbow movement (Curt et al., 2002a; Lotze et al., 1999, 2006; Shoham et al., 2001). Lower limb motor tasks included foot movement (Alkadhi et al., 2005; Astolfi et al., 2007; Cramer et al., 2005, 2007; Fallani et al., 2007; Halder et al., 2006; Hotz-Boendermaker et al., 2008; Lacourse et al., 1999; Lotze et al., 1999; Turner et al., 2001; Winchester et al., 2005) and toe movement (Castro et al., 2007; Green et al., 1998, 1999; Sabbah et al., 2002; Shoham et al., 2001; Winchester et al., 2005). Facial motor tasks included lip movement (Astolfi

et al., 2007; Fallani et al., 2007; Green et al., 1998; Lotze et al., 1999; Mattia et al., 2006; Shoham et al., 2001) and tongue movement (Curt et al., 2002a; Mikulis et al., 2002; Turner et al., 2001). Imagined movement was also investigated in some studies and included lower limb movement (Alkadhi et al., 2005; Cramer et al., 2005; Hotz-Boendermaker et al., 2008; Lacourse et al., 1999; Lotze et al., 1999; Sabbah et al., 2002) and upper limb movement (Lacourse et al., 1999; Sabbah et al., 2002).

Self-paced versus cued motor tasks

The rate of movement used in motor activation tasks also differed across studies and included 3 Hz (Turner et al., 2003); 1 Hz (Lotze et al., 2006); 0.5 Hz (Alkadhi et al., 2005; Curt et al., 2002a; Winchester et al., 2005); self-paced (Astolfi et al., 2007;

Hotz-Boendermaker et al., 2008; Jurkiewicz et al., 2007; Mattia et al., 2006; Mikulis et al., 2002; Sabbah et al., 2002; Turner et al., 2001); 40/60 movements/min (Lotze et al., 1999); 40 beats/min (Bruehlmeier et al., 1998; Curt et al., 2002b); every 6–10 s (Fallani et al., 2007; Green et al., 1998, 1999); and every 3 s (Cramer et al., 2007). Rate of movement was not specified in a subset of studies (Castro et al., 2007; Cramer et al., 2005; Halder et al., 2006; Lacourse et al., 1999; Shoham et al., 2001), and thus it was assumed that the movement rate in these articles was self-paced. Force of movement was specified in two studies where movement was performed at either a high or low force level (Cramer et al., 2005) or at 20%, 40%, and 75% of measured maximum voluntary contraction (Halder et al., 2006). Force was not relevant in some studies because not all movement was performed against resistance.

Brain activation patterns in SCI

Different findings of comparisons of brain activation magnitude between individuals with SCI and controls occurred between studies. Table 1 summarizes studies that reported increased, decreased, or unchanged activation during movement in individuals with SCI compared to controls ($n = 11$ studies). Specifically, nearly half (5/11) of the studies reporting changes in activation magnitude showed a significant increase in activation of motor areas. Common areas of increased brain activation in individuals with SCI compared to controls during movement are shown in Figure 2 (Alkadhi et al., 2005; Bruehlmeier et al., 1998; Curt et al., 2002a, 2002b; Hotz-Boendermaker et al., 2008). Specifically, the cortical areas that showed increased activation were bilateral primary motor cortex (M1), supplementary motor area (SMA), premotor area (PM), cingulate motor area (CMA), parietal cortex, and contralateral primary somatosensory cortex (S1). Activation in these cortical areas of individuals with SCI consisted of both an increased intensity of activation above that found in controls as well as novel activation (i.e., activation of an area in SCI that was not activated in controls). Subcortical areas, such as bilateral cerebellum, thalamus, and basal ganglia, repeatedly showed novel activation in individuals with SCI compared to controls (Alkadhi et al., 2005; Bruehlmeier et al., 1998; Cramer et al., 2005; Curt et al., 2002b; Hotz-Boendermaker et al., 2008). In contrast to findings of increased brain activation, 3/11 of the reviewed studies reported a pattern of activation in individuals with SCI that was similar to controls (Castro et al., 2007; Halder et al., 2006; Mattia et al., 2006). Another 2/11 of the studies reported reduced activation in individuals with SCI when compared to controls but did not have explicit analysis to statistically determine whether the activation was altered (Cramer et al., 2005; Sabbah et al., 2002). These studies involved a mix of active and imagined movement protocols and were cross-sectional in design.

Time profile of cortical reorganization

Although most of the SCI studies were cross-sectional, Jurkiewicz et al. (2007) used a longitudinal design to examine brain activation during wrist extension of individuals with American Spinal Injury Association Impairment Scale (AIS) A-D, C5–8 injury, beginning as early as 1 week post-injury and ending at 1 year after injury. These authors reported that initially, in the subacute phase after injury, individuals with

SCI had reduced activation within M1 and greater activation in secondary motor areas (e.g., SMA, CMA, PM, and posterior parietal cortex) compared to that of controls (Jurkiewicz et al., 2007). However over time, as recovery progressed into the chronic phase, there was a progressive increase in M1 activation and decrease in secondary motor area activation in individuals with SCI until activation was similar to that of controls (Jurkiewicz et al., 2007).

Spatial shift in region of brain activation in SCI

Some studies found a distinct spatial shift of activation in individuals with SCI compared to controls. Table 2 summarizes these articles and Figure 3 depicts examples of the two types of spatial shift in activation found. Specifically, five studies found a posterior shift in activation in individuals with SCI (AIS A-D) compared to that of controls (Cramer et al., 2005; Green et al., 1998, 1999; Shoham et al., 2001; Turner et al., 2003). These studies included imagined foot movement (Cramer et al., 2005), and attempted finger (Green et al., 1998, 1999), toe (Green et al., 1998, 1999), hand (Shoham et al., 2001; Turner et al., 2003), and elbow (Shoham et al., 2001) movements in individuals with tetraplegia and paraplegia ranging from 9 months to 5 years post-injury. For example, Turner et al. (2003) employed fMRI to show that a posterior shift for hand motor representation occurs in complete thoracic or lumbar individuals with SCI during intact finger movement. Interestingly, these same authors demonstrated that the sensory representation did not undergo a similar shift during movement (Turner et al., 2003). Using EEG, Green and colleagues (1999) showed that after SCI (AIS A-D), attempted index or middle finger movements were mapped to a posterior location in 22/24 individuals with tetraplegia compared to controls whereas only 9/20 individuals with paraplegia had posterior motor potentials (MPs) with actual or attempted movements. Furthermore, these authors observed that 100% of individuals with paraplegia who could move their toes had posterior MPs, whereas fewer than 27% of individuals with complete paralysis had posterior MPs (Green et al., 1999), indicating a relationship between posterior reorganization and completeness of injury in individuals with paraplegia.

Another four studies demonstrated that activation was displaced in the direction of the deafferented limb representation of individuals with SCI (AIS A-C) rather than posteriorly (Bruehlmeier et al., 1998; Lotze et al., 1999, 2006; Mikulis et al., 2002). These studies too included a range of motor tasks from upper limb movement (Bruehlmeier et al., 1998; Lotze et al., 1999, 2006), to tongue movement (Mikulis et al., 2002) in subacute and chronic individuals with tetraplegia and paraplegia. For example, Bruehlmeier et al. (1998) showed that during attempted hand movement of paralyzed muscles caudal to the lesion as well as intact muscles rostral to the lesion, there was a shift of hand activation into the deafferented leg representation of the SMC in cervical and thoracic/lumbar SCI. Using a tongue movement task, Mikulis and colleagues (2002) showed that the site of maximum M1 activation during intact tongue movement was shifted to the direction of the deafferented upper limb representation in individuals with AIS A-B. Interestingly, these authors also observed a strong correlation between the level of SCI and shift of tongue representation, where the maximum activation

TABLE 1. COMPARISONS OF SUBJECTS, MODALITY, MOTOR TASK AND FINDINGS ACROSS STUDIES DEMONSTRATING BRAIN ACTIVATION DIFFERENCES IN SCI SUBJECTS COMPARED TO CONTROLS

<i>Author</i>	<i>Subjects (no.)</i>	<i>Injury location, completeness, time post</i>	<i>Modality and motor task</i>	<i>Activated anatomical areas in SCI vs controls</i>
Hotze-Boendermaker et al. (2008)	9	T-L, ASIA A-B, 2–20 yr	fMRI; imagined and attempted/ executed right foot flexion (30°–0°–45°) at a self-paced rate of ~0.5 Hz	During execution, increased activation in contralateral PMv, putamen/pallidum, bilateral superior and inferior parietal lobules, PFC, cerebellum. During imagination, increased activation in bilateral SMA, CMA, PMv, inferior parietal lobule, PFC, thalamus, putamen/pallidum, ipsilateral cerebellum.
Alkadhi et al. (2005)	8	T3-L1, ASIA A, 4–76 mo	fMRI; imagined right foot flexion-extension at a rate of ~0.5 Hz	Increased activation in contralateral M1 and S1 foot representation, bilateral SMA, pre-SMA, CMA, PMd, PMv, superior and inferior parietal regions, S2, insular cortex, PFC, putamen, caudate nucleus, thalamus and cerebellum.
Curt et al. (2002a)	9	T-L, ASIA A-B, 4–106 mo	fMRI; self-paced right limb movements at ~0.5 Hz: repetitive wrist flexion (40°), extension (20°); elbow flexion (100°)-extension ($\pm 30^\circ$); repetitive, sequential finger-thumb opposition	Enlargement of M1 activation volume during finger movements. Increased activation of bilateral SMA and PM, contralateral S1, bilateral superior parietal lobe, contralateral inferior parietal lobe, and bilateral cerebellum during movements of the fingers. Also fewer but similar areas show increased activation during wrist and elbow movement.
Curt et al. (2002b)	14	C- T-L, ASIA A, 0.3–9.9 yr	PET; right wrist extension 40 times/min; force of wrist extension was recorded via semiconductor installed in a bar attached to the back of the hand (integral force \times time; $N\times s$).	In individuals with paraplegia: contralateral SMC and thalamus, ipsilateral superior parietal lobe, and bilateral cerebellum showed increased activation. In individuals with tetraplegia, increased upper limb deficits related to decreased activation of contralateral SMC, SMA, and ipsilateral cerebellum.
Bruehlmeier et al. (1998)	14	C- T-L 0.3–9.9 yr	PET; repetitive joystick movements of the right hand in 4 different directions; movements externally triggered at 40 beats/minute	Additional activation in individuals with SCI. Individuals with tetraplegia: bilateral thalamus, ipsilateral putamen, contralateral insula, ipsilateral parietal. Individuals with paraplegia: bilateral thalamus, bilateral putamen, ipsilateral pallidum, contralateral cerebellum, ipsilateral parietal.
Cramer et al. (2005)	12	$\geq T6$, ASIA A, >1 yr	fMRI; R foot movement (attempted and imagined); subjects watched videos of 30 s rest (foot at rest) alternated with 30 s active state (foot hovering above object). During active state, subjects either imagined or attempted movement completion. Each 30 s active state was all low-force or all high-force	Additional activation in individuals with SCI in contralateral superior temporal gyrus during imagined movement. Novel activation in individuals with SCI in contralateral globus pallidus during attempted movement. Also, individuals with SCI showed reduced activation volume compared to controls, but this latter result not statistically confirmed.

(continued)

TABLE 1. CONTINUED

<i>Author</i>	<i>Subjects (no.)</i>	<i>Injury location, completeness, time post</i>	<i>Modality and motor task</i>	<i>Activated anatomical areas in SCI vs controls</i>
Sabbah et al. (2002)	9	T-L, ASIA A-B, 1 month–33 yr	fMRI; attempted and imagined sequential finger tapping against thumb with both hands simultaneously; attempted and imagined repeated flexion-extension of left and right toes simultaneously. Self-paced rate.	Results not statistically confirmed: observed activations of reduced amplitude during attempted and imagined toe movement in individuals with SCI. Activation areas in perioral regions were larger in 6/9 individuals during attempted and imagined finger movement.
Mattia et al. (2006)	7	C ASIA A/C, Avg. 18.4 ± 6 mo	EEG; brisk protrusion of lips repeated every 6–7 s in a self-paced manner	No significant differences between groups. Activation in motor areas had preserved temporal and spatial pattern during preparation and execution of intact movements.
Halder et al. (2007)	10	T-L, ASIA A-B, 1–15 yr	EEG; Sphygmomanometer bulb placed between sole of R foot and floor. Subjects were instructed to keep heel on floor and squeeze or attempt to squeeze down bulb at 20, 40, and 75% MVC, using ankle movements, and release as fast as possible.	No significant group differences in timing of motor cortical activation. No significant group differences in cortical modulation of higher force levels, but differences found at low forces with no reliable modulation in individuals with SCI.
Castro et al. (2007)	10	complete, 2–5 mo	EEG; Subjects were instructed to prepare to flex and extend abruptly all the toes of the appropriate foot before each tone and once tone was heard to attempt to conduct, or conduct, the motor act	No significant differences between groups in readiness potential and no overall group differences in motor potential interval. Reported that readiness potential in individuals with SCI is more similar to controls that execute movement, while motor potential is more similar between individuals with SCI and controls that did not execute movement. Reported decreased activation in M1 and increased activation in secondary sensorimotor areas in subacute stage (results not statistically confirmed). With recovery and time post-SCI, activation increased significantly in M1 (from first to last session) and decreased in secondary areas until it was similar to controls.
Jurkiewicz et al. (2007)	6	C, ASIA A-D, 0.25–6 mo; SCI subjects were studied over the course of the first year post-injury, with testing at 4 time points	fMRI; R wrist extension consisting of repeated alternating contraction and relaxation during each movement block. Movements were self-paced.	

C, cervical; T, thoracic; L, lumbar; R, right; L, left; M1, primary motor cortex; S1, primary sensory cortex; S2, secondary sensory cortex; SMC, sensorimotor cortex; SMA, supplementary motor area; PM, premotor cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PFC, prefrontal cortex; CMA, cingulate motor area.

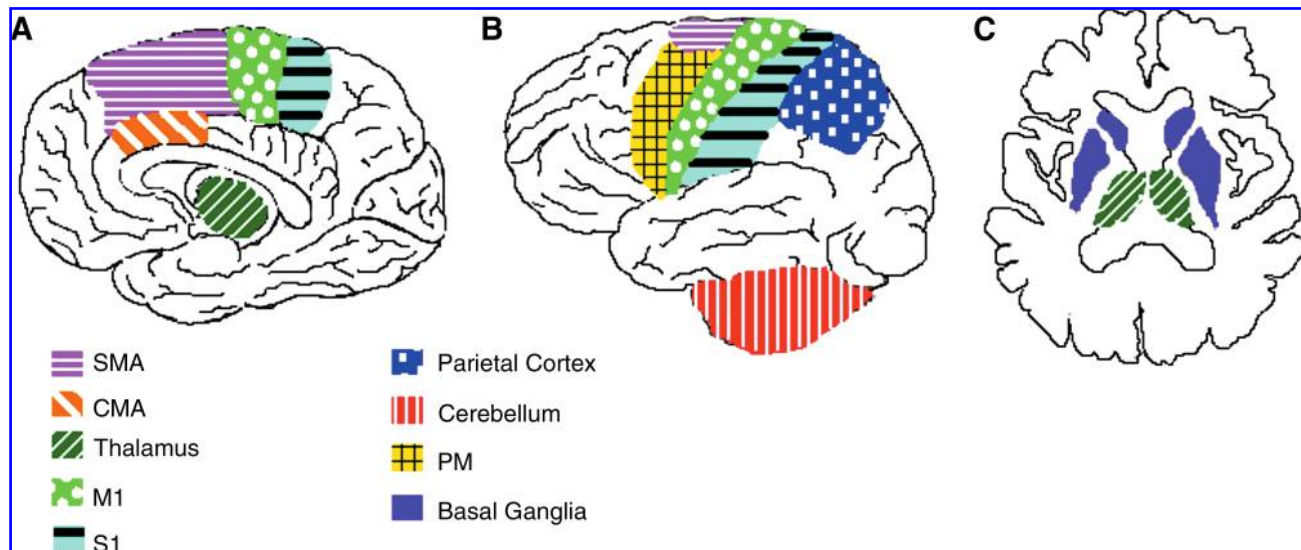


FIG. 2. Brain areas with increased activation during a motor task in SCI compared to controls. Increased activation was found in bilateral M1, S1, SMA, PM, CMA, parietal cortex, cerebellum, thalamus, and basal ganglia. (A) Medial view. (B) Lateral view. (C) Axial view.

moved more medially, superiorly, and posteriorly with higher levels of injury (Mikulis et al., 2002).

Influence of level of injury on brain activation

In individuals with a complete thoracic or lumbar level SCI, increased brain activation was found during imagined foot movements (Alkadhi et al., 2005; Hotz-Boendermaker et al., 2008), and during intact wrist (Curt et al., 2002a, 2002b) and finger and elbow movements (Curt et al., 2002a). These studies, however, included individuals with only paraplegia. Moreover, Curt et al. (2002b) found greater activation in contralateral SMC, contralateral thalamus, bilateral cerebellum, and ipsilateral parietal cortex in individuals with complete paraplegia compared to controls while complete tetraplegia showed much less brain activation in motor areas compared to control and individuals with paraplegia. Bruehlmeier et al. (1998) found that during a hand motor task performed with intact (paraplegia) or paralyzed (tetraplegia) muscles, both individuals with paraplegia and tetraplegia showed increased activation of contralateral SMC and SMA, ipsilateral cerebellum, bilateral thalamus, and basal ganglia compared to that of controls. However in all the areas with additional activation, the strength of activation differed in relation to the level of the SCI, where increased brain activation was related to higher lesion levels (Bruehlmeier et al., 1998).

Influence of intervention on brain activation in SCI

Two studies included in this review used fMRI to examine neural activation before and after a type of intervention. Specifically, Cramer et al. (2007) used motor imagery (MI) training as an intervention in chronic, complete individuals with tetraplegia ($n=6$) and paraplegia ($n=4$). Subjects underwent behavioral, fMRI, and TMS testing on day 1, followed by 7 days of home motor imagery training for their right foot and tongue, followed by all testing again on day 9.

The results from this study demonstrated that MI significantly improved motor performance and was associated with increased activation in the contralateral globus pallidus in MI-trained individuals with SCI and contralateral putamen in MI-trained individuals with SCI and healthy individuals compared to healthy individuals that did not receive MI training. Winchester et al. (2005), through a small sample case series, examined brain activation during foot and toe movement before and after body weight supported treadmill training that consisted of a combination of a Lokomat and Woodway treadmill for 1 h three times per week for 12 weeks. They found that individuals with incomplete paraplegia (14 weeks to 48 months post-SCI at start of intervention) showed increased activation in sensorimotor cortex ($n=3$) and cerebellar regions ($n=4$) after intervention. Moreover, improvement in locomotion (e.g., change in Walking Index for Spinal Cord Injury II (WISCI II), improved over-ground gait speed) appeared to be accompanied by increased activation of the cerebellum (Winchester et al., 2005). However, the sample size was too small to be definitive, and without a control group for comparison, one cannot rule out the contribution of spontaneous recovery to the changes observed in this subacute group.

Discussion

Mechanisms of reorganization after SCI

Reorganization of cortical networks in the brain can occur spontaneously after neurological injury. Although SCI does not involve direct injury to cortical neurons, a spinal cord lesion affects primary sensorimotor areas connected to the lesioned area and can result in reorganization of these and surrounding regions in order to compensate for sensorimotor loss (Donoghue et al., 1990; Jain et al., 1997). The brain reorganization that occurs can be dependent on both structural and functional changes in the brain. Some structural changes may include synaptic alterations such as the change in length

TABLE 2. COMPARISONS FOR SUBJECTS, MODALITY, MOTOR TASK AND FINDINGS ACROSS STUDIES DEMONSTRATING A DISTINCT SHIFT IN MOTOR ACTIVATION

<i>Author</i>	<i>Subjects (no.)</i>	<i>Injury location, completeness, time post</i>	<i>Modality and motor task</i>	<i>Findings</i>
Cramer et al. (2005)	12	≥ T6, ASIA A, >1 yr	fMRI; R foot movement (attempted and imagined); subjects watched videos of 30 s rest (foot at rest) alternated with 30 s active state (foot hovering above object). During active state, subjects either imagined or attempted movement completion; Each 30 s active state was all low force or high force	Results not statistically confirmed: posterior shift in contralateral SMC activation site of 20 mm was present during imagined movement
Green et al. (1998)	12	C-T, ASIA A-D, >9 mo	EEG; Subjects who could generate EMG activity rapidly flexed/extended middle finger, dorsiflexed toes, or pursed lips every 7–10 s. Subjects who couldn't generate EMG activity attempted finger or toe movement.	Individuals with tetraplegia (n = 7) had more posterior MPs than controls during finger movements. One individual with paraplegia able to move his toes had posterior MPs with toe and finger movement
Green et al. (1999)	44	C-T, ASIA A-D, 1–336 mo	EEG; Subjects who could generate EMG activity rapidly flexed/extended middle finger, dorsiflexed toes every 7–10 s. Paralyzed subjects who could not generate EMG activity attempted paralyzed finger or toe movement.	MPs with finger movements were mapped to a posterior location in 22/24 individuals with tetraplegia compared to controls and 9/20 individuals with paraplegia had a posterior MP location with actual or attempted toe movements.
Turner et al. (2003)	13	T2-L1, complete, >5 yr	fMRI; 4-finger right hand movement at 3 Hz (via visual cue). Movement consisted of tapping all 4 fingers against the palm of the hand in a squeezing motion	Individuals with SCI had increased proportion of subjects that showed AM posterior to central sulcus.
Shoham et al. (2001)	5	C, >1.5 yr	fMRI; repeated movement or attempted movement of fingers (adduction-abduction of the fingers), elbows (flexion), toe (flexion), left knee (extension) and lips (pursing)	Results not statistically confirmed: Consistent dorsoposterior shift of hand and elbow AM, but similar shift in hand knob, indicating it may be due to intergroup anatomical differences.
Lotze et al. (2006)	6	T or L, ASIA A-C, 6–1776 wk	fMRI, TMS; pinch grip or lift 160g weight with right hand (TMS); right elbow movement (45° against gravity and extension with gravity) or thumb movement (flexion and relaxation) performed at 1 Hz (fMRI)	Displacement of elbow movement representations in M1 into the direction of the deafferented cortical thoracic representation for individuals with complete SCI only (n = 5).
Lotze et al. (1999)	4	T3, T7, T9, L1; complete and incomplete, 6–1456 wk	fMRI; Right elbow (4 patients), right thumb (4 patients), lip (2 patients) and imagined (3 patients) and executed (1 patient) right foot (lifting foot) movement. Executed tasks had a rate of 60, imagined tasks had a rate of 40 movements/min	Individuals with complete SCI (n = 3) showed a displacement of the AM in contralateral M1 during elbow movement; the individual with incomplete SCI showed no displacement of elbow AM
Mikulis et al. (2002)	11	C, ASIA A-B, >5.5 mo	fMRI; flexed and extended the wrist at a rate of 1 cycle/second for 15 seconds, tongue movement consisted of tapping of the upper incisors at 1 cycle/second for 15 seconds. Movements were self paced	During tongue movement, the site of maximum left M1 activation was shifted superior and medial, into direction of upper limb representation adjacent to deafferented area. Right M1 activation shifted only in the medial direction.
Bruehlmeier et al. (1998)	14	C/T-L, 0.3–9.9 yr	PET; repetitive joystick movements of the right hand in 4 different directions; movements externally triggered at 40 beats/min	Expansion of hand activation into deafferented leg area of SMC

C, cervical; T, thoracic; L, lumbar; AM, activation maxima; MP, motor potential; SMC, sensorimotor cortex; SMA, supplementary motor area; M1, primary motor cortex; Pt, patient.

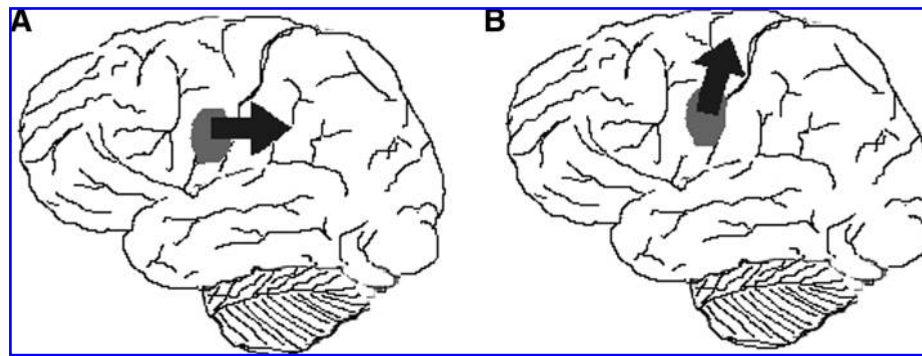


FIG. 3. Depictions of the brain showing two types of spatial shift in activation described during a motor task in paraplegic and tetraplegic SCI subjects compared to controls. (A) Posterior shift of activation towards S1 during an upper limb motor task (activation represented by shading). (B) Activation of facial/upper limb movement is shifted in the direction of the deafferented upper/lower limb representation in para/tetraplegic SCI subjects.

and diameter of existing dendritic branches or the growth of new branches, providing the opportunity for new synapses (Bayona et al., 2005). Functionally, changes may include modification of neuronal activity, synaptic efficacy (Dunlop, 2008), or increases in astrocytic activity (Kolb et al., 1995).

Regarding reorganization of the brain, it is important to note that although reorganization after injury provides the opportunity for recovery of function (Wolpaw, 2007), this reorganization does not always equate to improved motor recovery. However, rehabilitation interventions are one modality that may provide an opportunity to induce and guide recovery of function, as in the study by Winchester et al. (2005), in which a body weight supported treadmill program increased brain activation, as well as improved walking ability in people with SCI. It is critical to note that reorganization will be different in individuals with paraplegia compared to those with tetraplegia during upper limb movement. Brain activation with upper limb movements in individuals with paraplegia involve the intact arms/hands that are above the level of lesion, whereas brain activation in individuals with tetraplegia will involve attempted or imagined movement below the level of lesion.

Influence of SCI on reorganization of brain activation

Differences were demonstrated between studies in terms of comparisons of brain activation magnitude between individuals with SCI and controls, where some reported statistically increased activation and others reported no statistical change in activation after SCI. The source of the differences between these studies could be attributed to the varying subject characteristics since activation appears to depend on the lesion level (Bruehlmeier et al., 1998; Curt et al., 2002b) and time after injury (Jurkiewicz et al., 2007). Curt et al. (2005b) have also shown a differential impact of spinal lesion and functional impairment on brain activation. Results from their studies suggest that changes in brain activation may be influenced by the spinal cord lesion itself, as in individuals with complete paraplegia during normal hand movement, or may be influenced by the amount of deficit, as in individuals with complete tetraplegia where reduced activation occurs with more impaired hand movement (Curt et al., 2002b).

In addition, studies involved imaginary and attempted movement of a body part below the level of SCI, and executed

movement of a body part above the level of the lesion. As the lower limbs are always below the level of injury in individuals with paraplegia and tetraplegia, attempted movement of the lower limbs would involve absent or reduced motor output, force, and afferent feedback. Both fMRI and PET studies have demonstrated that increased activation occurs in M1, SMA (Cramer et al., 2002; Dettmers et al., 1995, 1996), PM, and cerebellum (Dai et al., 2001), with increasing force in healthy individuals. Thus, with differences in force output between studies due to motor tasks, it is likely that reduced activation would occur in subjects producing less force. In fact, this has been observed by Curt et al. (2002b) where individuals with complete tetraplegia with reduced force of wrist extension and decreased upper limb sensorimotor scores showed significantly reduced activation of the contralateral SMC.

Unfortunately, it was not possible to draw definitive conclusions as to the differing factors between those studies that showed increased activation ($n = 5$) versus those that showed no change in activation ($n = 4$). The studies in each group had a mix of individuals with complete/incomplete, chronic/subacute, and tetraplegia/paraplegia. It is difficult to determine the influence of SCI on brain reorganization due to inclusion of individuals with varying lesion locations, completeness of injury, and time after injury. Thus, in the future, the use of uniform subject groups should be attempted to more precisely determine patterns of brain reorganization after varying types of SCI.

Shift in region of brain activation after SCI

When comparing activation of individuals with SCI to controls, one similarity reported among studies was a shift in M1 activation either posterior in direction, or in the direction of the deafferented limb representation (see Fig. 3). Green et al. (1999) have proposed an explanation for the posterior shift of activation observed in individuals with SCI. They suggest that after SCI there is an increased loss of axons in M1 and surviving axons from S1 may contribute to the damaged corticospinal tract, resulting in increased activity in S1 and a posterior shift of activation (Green et al., 1999). They postulate that the S1 axons may be less vulnerable to trauma because they run more medial and posterior than M1 axons (Green et al., 1999). Turner et al. (2003) suggest that it could also be possible that a posterior shift relates to increased activation in

S1 due to neuropathic pain experienced by some people with SCI. Unfortunately, neuropathic pain was not measured in any of the studies, so whether the shift in S1 represents motor output or somatosensory processing has yet to be determined. Future studies recording somatosensory evoked potentials are needed (Cramer et al., 2005) to elucidate the role of S1 after SCI.

The contrasting shift in activation in the direction of the deafferented limb representation, reported by some studies, may be explained by chronicity of SCI. For example, Lotze et al. (2006) have found that activation displacement toward the deafferented limb representation in individuals with SCI (AIS A-C) correlates significantly with the time since SCI while displacement is minimal in individuals tested a year or less after SCI. However, posterior motor potentials have been found in individuals with AIS A-D 4–6 weeks after injury (Green et al., 1999). Moreover, in a subset of patients, Green et al. (1999) found that as recovery progresses, initial posterior motor potentials begin to move more anterior. Thus, it could be that shifts in activation are dynamic and that posterior reorganization toward S1 occurs initially after injury and moves more anterior and towards the deafferented limb representation in M1 as duration of SCI progresses. The changes early after injury may reflect the immediate involvement of secondary motor areas to develop new motor strategies. However, this explanation may be lacking given the posterior shift in activation in chronic (>1 year) individuals with SCI (Cramer et al., 2005; Shoham et al., 2001; Turner et al., 2003). These individuals mostly had complete SCI (24/25 subjects) (Cramer et al., 2005; Turner et al., 2003), suggesting that individuals with complete SCI, having total disruption of fibers traveling through the spinal cord, may have activation shifted posteriorly rather than anteriorly.

Alternatively, the shift in brain activation may be influenced by level of SCI (Bruehlmeier et al., 1998). In the present review, studies having a posterior shift in activation had a majority of individuals with a thoracic injury level or higher (70/83 subjects) while those studies demonstrating a shift of activation into the deafferented leg representation had a majority of individuals with lesions at the thoracic level or lower (24/36 subjects), indicating that the type of activation shift occurring after SCI may depend on level of injury. The exact mechanisms of how level or completeness of injury may affect brain reorganization is not exactly known. One possibility stems from the fact that the completeness and level of injury affect the amount, quality, or influence of afferent input that feeds back to the cortex. It is well established that afferent feedback is important in motor control. Past authors have proposed that the central nervous system (CNS) can use afferent information to aid internal commands in the driving of output motor neurons or, alternatively, to inform the CNS about errors in movement execution (Nielsen and Sinkjaer, 2002). At the level of motor neurons, past research has shown that blocking proprioceptive muscle afferent signals decreases the voluntary firing rates of motoneuron pools (Macefield et al., 1993), and this may affect sustaining motor activity of a set of muscles (Gandevia et al., 1990). From a motor function standpoint, individuals with deafferentation often are incapable of accurately performing complex movements requiring coordination between several joints (Jeannerod et al., 1984) and controlling force output (Jeannerod et al., 1984; Nowak et al., 2003). This past research is just a sample of the

evidence establishing the importance of sensory afferent feedback to movement.

Importantly, there is also evidence that the amount of somatosensory input can affect changes in activation in cortical motor areas. For example, decreasing sensory input through ischemic nerve block results in changes such as increased amplitudes of MEPs (Brasil-Neto et al., 1992; Ziemann et al., 1998) and enlarged contralateral motor cortical maps to the muscle being tested (Brasil-Neto et al., 1993). In addition, ischemic nerve block of one hand can lead to reorganizational changes in the motor cortex contralateral to the deafferented one (Werhahn et al., 2002). Increasing sensory input by local muscle vibration can also cause changes in the contralateral motor cortex, such as augmented MEPs (Kossev et al., 1999), and can also lead to reorganizational changes affecting the contralateral hand muscles, such as decreases in MEPs and increases in interhemispheric inhibition onto contralateral hand muscles (Hamdy et al., 1998).

As the completeness and level of injury affect the amount of afferent input that feeds back to the cortex after SCI, this combined evidence suggests that the amount of sensory preservation occurring due to the nature of the injury can influence brain activation after SCI.

Comparison of reorganization of brain function in SCI with other CNS damage

Distant neuronal injury caused by SCI resulted in increased recruitment of secondary motor areas similar to findings found with individuals having direct neurological disorders of the brain such as stroke, multiple sclerosis, ALS (Weiller et al., 2006), and Parkinson's disease (Ceballos-Baumann, 2003). For example, increased brain activation has occurred in individuals with stroke compared to healthy controls in the contralesional SMC and PM, ipsilesional cerebellum, SMA (Cramer et al., 1997), PFC, CMA, parietal cortex, and basal ganglia (Weiller et al., 1992). This review demonstrates that many of these same areas also show increased brain activation in people with SCI (see Fig. 2). In stroke, it is suggested that the amount of reorganization relates to the amount of damage caused by the lesion in the brain (Teasell et al., 2005). Yet this cannot apply to individuals with SCI having an intact brain, begging the question of why individuals with SCI and stroke share several aspects of brain reorganization following injury when they involve strikingly different mechanisms of injury. One possibility is that the changes observed are due to deafferentation and de-efferentation following injury. Merzenich et al. (1984) have demonstrated that after deafferentation in primates, reorganization of the sensory cortex occurs, and similarly Donoghue et al. (1990) have shown that after motor nerve transection in rats, reorganization of the motor cortex occurs. Likewise, as mentioned, in humans the influence of afferent input on changes in activation in cortical motor areas has also been demonstrated (e.g., Hamdy et al., 1998; Swayne et al., 2006).

Alternatively, the use of an internal representation or model by the CNS for control of motor output has been proposed (Flanagan and Wing, 1997; Wolpert et al., 1995), and thus it may be that injury caused by stroke and SCI produces common changes to such an internal representation, resulting in similar types of reorganization of brain function. Following this, reorganization after stroke appears to partly depend on

secondary motor areas that have structural connections with the injured area (Teasell et al., 2005), and this review shows that SCI too involves reorganization dependent on areas, such as M1, S1, SMA, and PM, that have connections to the injured area (spinal cord) via corticospinal tracts. Yet, this reorganization after SCI appears to be more dependent on intact pyramidal tracts, whereas reorganization after stroke also depends on extrapyramidal tracts.

Research on reorganization after stroke has gone a step beyond documenting brain activation during spontaneous recovery and has established that active rehabilitation can change brain plasticity and promote functional recovery after injury. Although a number of rehabilitation strategies for SCI, such as motor imagery (Cramer et al., 2007), resistance training (Gregory et al., 2007), and locomotor training (Hicks et al., 2005; Wirz et al., 2005), have emerged, only two studies were found that demonstrated reorganization of brain function dependent on rehabilitation (Cramer et al., 2007; Winchester et al., 2005). Moreover, no studies were found that examined the effects of intensity and timing of rehabilitation on reorganization of brain function after SCI.

Preservation of brain motor control in complete SCI: Implications for basic science research

Similar cortical motor areas were recruited in complete individuals with SCI compared to controls during imagined and/or attempted movement. Even in individuals with chronic (>10 years after incident), complete paralysis of the lower limbs, activation patterns were modulated in protocols involving “attempt to move the foot” or “imagination of foot movement” (Hotz-Boendermaker et al., 2008), as well as attempts to move the foot with different forces (Halder et al., 2006).

The finding of preservation of brain motor control after complete SCI has important implications for basic science research. A variety of experimental therapies are emerging to promote regeneration of the injured spinal cord, including the application of neurotrophic factors (Kwon et al., 2002), drug therapy (Baptiste and Fehlings, 2006), and cell-based therapies (Guest et al., 2006). If regeneration of the injured spinal cord, and thus reconnection of the brain to the muscles, is possible, it is vital that the brain must still be able to activate in a way that will generate movement. Indeed, our systematic review demonstrated that even in individuals with complete, chronic SCI, the brain is still capable of appropriately activating and controlling functional motor programs in primary, as well as secondary motor areas after SCI.

Future directions

Further use of neuroimaging methods to assess the reorganization of brain networks after SCI is needed to distinguish typical patterns of reorganization from changes that might be unexpected (in time, area of activation, amount of activation), and to describe specific or new patterns of reorganization. In addition, it is imperative to gain knowledge of any maladaptive reorganization after SCI that might be associated with harmful or adverse effects.

From our systematic review, only two studies demonstrated reorganization of brain function after intervention (Cramer et al., 2007; Winchester et al., 2005) and no studies examined the effects of intervention factors (e.g., intensity,

timing) on reorganization of brain function after SCI. Even though neuroimaging techniques have provided researchers with the potential to examine possible plasticity behind therapeutic intervention, there is a lack of current knowledge in treatment effects on brain function in SCI. This is less than desirable as different interventions may reduce, or differentially impact, the physiological extent of reorganization. Thus, future research should aim to determine the impact of interventions, and various factors of interventions (timing, intensity), on brain reorganization after SCI.

In addition, findings of this review suggest that patterns of brain activation after SCI are dynamic and can change with recovery (Jurkiewicz et al., 2007), as well as with intervention (Cramer et al., 2007; Winchester et al., 2005). Thus, future research should aim to distinguish changes in reorganization that are based on intervention, such as cell transplants or pharmacology, from changes that reflect spontaneous recovery. Moreover, research should attempt to elucidate the dynamic nature of brain reorganization and its relation to functional outcome in both spontaneous recovery and the use of interventions. More specifically, it is likely that shifts in brain activation after SCI are dynamic, where activation of secondary areas occurs initially after injury and moves toward M1 as duration of SCI increases. The activation of secondary areas early after injury may reflect increased motor planning and use of new motor strategies. As these new strategies are learned, activation appears to shift to primary motor areas more typically involved in movement. This has implications for recovery of function and rehabilitation after SCI as it may provide a rational basis for implementation of types of motor training aimed to activate motor areas typically involved in movement. It would be useful for future research to clarify the relationship of brain reorganization, motor training and learning, and motor recovery after SCI.

Limitations

We did not include TMS studies for the reasons mentioned in the Methods and Materials section. However, Hoffman and Field-Fote (2007) recently used TMS to demonstrate an anterior shift of motor activation of the intact biceps brachii following training and somatosensory stimulation in one individual with chronic, complete SCI. Moreover, this shift in activation appeared to be associated with improved functional abilities. The data from this study extend the findings of this review, as it supports the idea that initially after SCI, a posterior shift in activation towards secondary areas occurs, but as recovery occurs, activation shifts anterior and back towards M1. However, in an earlier (Beekhuizen and Field-Fote, 2005) and later (Beekhuizen and Field-Fote, 2008) study, no such shift was found, although increased cortical excitability after training was reported in the latter study. The differences in these results may be due to limitations with using TMS to measure changes in cortical maps that are not present in other imaging modalities, such as fMRI. As Beekhuizen and Field-Fote (2005) acknowledge, MEPs are often measured at a single cortical location when two time points are used (e.g., before and after training). Unfortunately, if the site of maximal activation shifts to another location at the second time point, then this activation is likely to be missed with TMS measures. Furthermore, these studies assessed MEP threshold at rest (rather than with voluntary activation),

which may have introduced some variability. MEPs at rest do not reflect the same physiological processes as those during contraction and even slight background activity during a supposedly "rest" condition will affect the amplitude and latency of the MEP (Beric and Raghavan, 2004).

Summary

This systematic review found evidence that even distant neuronal damage, such as SCI, can result in reorganization of motor areas in the brain. Increased activation in secondary brain areas, and a distinct spatial shift in activation were the two key commonalities found across studies. Despite these similarities, differences in findings were apparent between studies that could be due to a variety of factors, such as time since injury, lesion level, completeness of injury, and amount of deafferentation. However, it is difficult to determine precisely the influence of these SCI factors on brain reorganization due to varying characteristics of subjects across, and even within, studies. Future studies should thus aim to evaluate uniform patient groups to more precisely determine patterns of brain reorganization after varying types of SCI. In addition, further neuroimaging research is needed to identify both typical and novel patterns of reorganization, maladaptive forms of reorganization, and the effects of interventions and spontaneous recovery on reorganization in relation to functional outcome after SCI.

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